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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,159	PAWLOWSKI ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *11-13 and 15-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/09/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group II, Claims 1-10, 14, CARD-12X (SEQ ID NO:15 encoding SEQ ID NO:16) in Paper of 01/06/04 is acknowledged and entered.

Claims 1-28 are pending in the instant application and Claims 11-13, 15-28 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Group II, Claims 1-10, 14, CARD-12X polynucleotide (SEQ ID NO:15 encoding SEQ ID NO:16) are currently under prosecution.

The traversal is on the following ground(s):

1) Applicants submit that a search of the isolated oligonucleotide claim 8 (Group 2) will overlap with a search of using the oligonucleotide in the method of claim 21 (Group 13). Applicants assert that in this regard, if the oligonucleotide of claim 8 is determined to be free of prior art, the use of the oligonucleotide the method claim 21 also will be free of prior art. Applicants submit that in view of the overlapping search relevant to claims 8 and 21, the Examiner would not be seriously burdened to search and examine the claims of Groups 2 and 13 together, and doing so would increase the efficiency of the search and examination process for this application.

2) Concerning the species election of Groups 1, 3, 4, 6, 7 and 9, Applicants traverse the sequence election requirement because a domain of a nucleotide or amino acid sequence is encompassed within the corresponding full length sequence and that accordingly, search and examination a full length sequence, including its domain(s), would not pose an undue burden on the Examiner.

Applicant's arguments have been considered, but are not found to be persuasive for the following reasons:

1) Concerning rejoining group 13 with group 2, group 13 would not be rejoined with group 2, because group 13 is different from group 2 as product and process. The inventions can be shown to be distinct if either or both of the following can be shown: (i) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the oligonucleotide product as claimed can be used in a materially different process such as for making a vector.

2) Concerning species requirement of full length sequence, and different domains thereof, the full length sequence and different domains thereof have different structure, and would require different searches. Therefore, it would be a serious burden for the Examiner to search of the species together.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, Group II, Claims 1-10, 14, CARD-12X polynucleotide (SEQ ID NO:15 encoding SEQ ID NO:16) are currently under prosecution.

OBJECTION

1. Claims 1-10, 14 are objected to, because parts of claims 1-10, 14 are drawn to non-elected inventions.

2. Claim 2 is objected to because claim 2 is confusing. It is not clear in claim 2 whether SEQ ID NO:16 is referred to the full length polypeptide sequence of CARD-12X or the CARD domain thereof. Similarly it is not clear in claim 2 whether SEQ ID NO:15 is referred to the full length polynucleotide sequence of CARD-12X or the CARD domain thereof.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8-10 are indefinite, because Claim 8 recites the limitation "said nucleic acid molecule". There is insufficient antecedent basis for this limitation in the claim.

REJECTION UNDER 35 USC 101, UTILITY

35 U.S.C. 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-10, 14 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility.

Claims 1-10, 14 are drawn to:

1) A nucleic acid molecule encoding the amino acid sequence of CARD-12X (the polypeptide of SEQ ID NO:16), or the polynucleotide of SEQ ID NO:15, (claim 1), or a nucleic acid molecule encoding a functional fragment of a CARD-containing polyppetide, wherein said nucleic acid molecule comprises the nucleotide sequence of the CARD domain of CARD-12X polynucleotide, or encoding the CARD domain of CARD-12X polypeptide (claim 2). Said nucleic acid molecule of claim 1 is cDNA or mRNA (claim 4),

2) A nucleic acid molecule that hybridizes to the nucleic acid molecule of claim 1 under moderately stringent hybridization conditions, or a nucleic acid molecule that hybridizes to the nucleic acid molecule of claim 2 under moderately stringent hybridization conditions, wherein said nucleic acid molecule does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37, and a composition comprising said nucleic acid molecule effective to inhibit expression of a CARD-containing polypeptide (claims 1-2, 7),

3) A nucleic acid molecule comprising substantially the same nucleotide sequence as SEQ ID NO:15 (claim 3),

4) A vector and a host cell containing the nucleic acid molecule of claim 1 (claims 5-6),

5) An oligonucleotide comprising at least 15 contiguous nucleotides of SEQ ID NO:15, or the complement thereof, wherein said nucleic acid molecule does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37,

wherein said oligonucleotide is labeled with a detectable marker, and a kit comprising said oligonucleotide (claims 8-10),

6) A method for producing a CARD-containing polypeptide (claim 14).

The specification discloses that CARD-12X protein is identified by BLAST search, using a representative of caspase recruitment domains (CARD domains) as queries (Example I on pages 84-86). The specification further discloses that CARD-containing polypeptide is so named for the ability of said CARD-containing polypeptide to bind caspases (p.7, first paragraph). The specification further discloses that CARD-containing polypeptides influence a variety of cellular and biochemical processes including apoptosis, by binding to the inactive form of capases and either activating or inhibiting caspases, or by binding to other proteins or by activating transcriptional factor NF-KB, or other CARD-containing polypeptides, and influencing cell adhesion, inflammation and cytokine receptor signaling (p.7, first paragraph, p.9, second paragraph).

The specification contemplates using CARD-12X for diagnosing and treating diseases characterized by an increased or decreased level of CARD-12X, such as neoplastic pathologies, autoimmune diseases or other pathologies related to abnormal cell proliferation or abnormal cell death, such as apoptosis (p.70-78). The specification discloses antibodies specific for CARD-12X for use in diagnosis of diseases or altering the activity of CARD-12X, or to block natural ligands from binding to CARD-12X (p.50-55).

However, neither the specification nor any art of record teaches what SEQ ID NO:15 is, what it does do; they do not teach a utility for any of the fragments claimed; they do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases.

The asserted utilities for SEQ ID NO:16 encoded by the claimed SEQ ID NO:15, such as production of and screening of agonists, antibodies and antagonists apply to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to SEQ ID NO:16.

Additional disclosed utilities for SEQ ID NO:15 include therapy and diagnosis of conditions and diseases such as cancer, or autoimmune diseases. However, there is no association between SEQ ID NO:15 and any disease. Additional work must be done to determine if SEQ ID NO:15 is differentially expressed in disease tissues as compared to normal cells and to determine if expression of SEQ ID NO:15 is associated with any disease state. The asserted diagnostic and therapeutic utility of SEQ ID NO:15 is based on the assumption that via the putative CARD-12X domain, the encoded polypeptide of SEQ ID NO:16 would bind to caspases and either activates or inhibits caspases. However there is no evidence that the putative CARD-12X domain of SEQ ID NO:16 would have the property of a CARD, conferring the binding ability to caspase, nor any evidence that after binding to caspases, SEQ ID NO:16 somehow could activate or inhibit caspases, a step necessary for inducing or inhibiting apoptosis. It is well known in the art that a CARD-containing polypeptide activates a caspase by forming a hetero-oligomer with the caspase and in this complex, the CARD-containing polypeptide

allosterically upregulates the caspase activity (Shiozaki E N, 2002, Proceed Natl Acad Sci, USA, 99 (7): 4197-202). It is also well known in the art that oligomerization of a caspase is induced by the CARD-containing polypeptide, and is required for casapse activation (Lee S H et al, 2001, J Biol Chem, 276(37): 34495-500). The specification however has not shown that the CARD-12X protein encoded by the claimed polynucleotide could induce the oligomerization of caspases upon interaction with caspases via the CARD-12X domain. Further, even if the putative CARD domain of the CARD-12X protein has the property of a CARD, one cannot predict that the CARD-12X protein could induce apoptosis, because not all CARD-containing polypeptides would induce apoptosis. For example, the CARD domain of the CARD-containing RAIDD polypeptide does not induce apoptosis upon overexpression (Shaerwin-Whyatt LM et al, 2000, Cell Death and Differentiation, 7: 155-165, especially page 162, first column). Moreover, there is no indication that the CARD-12X protein interacts and regulates NF-κB activation, or regulates cytokine processing, cytokine receptor signaling, caspase-mediated proteolysis, cytoskeletal integrity or anoikis, because there is no evidence that the putative CARD-12X domain has the property of a CARD domain, or regulates NF-kB activation, cytokine processing, cytokine receptor signaling, caspase-mediated proteolysis, cytoskeletal integrity or anoikis and because not any protein would regulate NF-kB activation, cytokine processing, cytokine receptor signaling, caspase-mediated proteolysis, cytoskeletal integrity or anoikis. Thus, it is not clear how one could use the claimed CARD-12X protein for diagnosis and treating disorders with undesirable high

or low rate of apoptotic cell death, or various inflammation disorders. Given the above, it is clear that the claimed invention does not have specific and substantial utility.

For reasons set forth above the disclosure satisfies none of the criteria for a specific, substantial utility *See In re Kirk*, 153 USPO 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.'). In *Brenner*, the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPO at 690. Here, there is no evidence that the claimed SEQ ID NO:58 or polynucleotide encoding SEQ ID NO:168 or the putative polypeptide encoded thereby has any utility.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a specific, substantial asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1-10, 14 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention for practical benefits.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 1-10, 14 are rejected under 35 USC 112, first paragraph.

Claims 1-10, 14 are drawn to:

1) A nucleic acid molecule that **hybridizes** to the nucleic acid molecule of claim 1 **under moderately stringent hybridization conditions**, or a nucleic acid molecule that hybridizes to the nucleic acid molecule of claim 2 under

moderately stringent hybridization conditions, wherein said nucleic acid molecule does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37, and a composition comprising said nucleic acid molecule effective to inhibit expression of a CARD-containing polypeptide. Said nucleic acid molecule is cDNA or mRNA (claims 1-2, 4, 7),

2) A nucleic acid molecule encoding a functional fragment of a CARD-containing polyppetide, wherein said nucleic acid molecule **comprises** the nucleotide sequence of the CARD domain of CARD-12X polynucleotide (claim 2),

3) A nucleic acid molecule comprising **substantially the same nucleotide sequence** as SEQ ID NO:15 (claim 3),

4) A vector and a host cell containing the nucleic acid molecule of claim 1 (claims 5-6),

5) An oligonucleotide **comprising** at least 15 contiguous nucleotides of SEQ ID NO:15, or the **complement** thereof, wherein said nucleic acid molecule does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37, wherein said oligonucleotide is labeled with a detectable marker, and a kit comprising said oligonucleotide (claims 8-10),

6) A method for producing a CARD-containing polypeptide, comprising expressing the cDNA of a nucleic acid molecule comprising **substantially the same nucleotide sequence** as SEQ ID NO:15 (claim 14).

The specification discloses that "moderately stringent hybridization" refers to conditions that permit target-nucleic acid to bind a complementary nucleic acid. The hybridized nucleic acid will "generally" have at least about 60%, 75%, 90% identity (p.32, last paragraph, bridging p.33).

The specification discloses that "substantially the same nucleotide sequence" refers to nucleic acids that hybridize to the reference polynucleotide under moderately or highly stringent conditions, or having at least 60%, 65%, ...or 99% identity to the reference nucleotide sequence (p.30, second paragraph).

It is noted that the claimed hybridizing nucleic acid molecules, or "substantially the same nucleotide sequence" as defined in the specification, encompass variants of SEQ ID NO:15, or variants of fragments thereof containing the CARD domain, with unknown structure, wherein said variants hybridize to SEQ ID NO:15 or fragments thereof containing the CARD domain via a common fragment, or have at least 60%, ...99% identity to SEQ ID NO:15.

It is further noted that claim 2 reciting an isolated nucleic acid encoding a functional fragment of a CARD-containing polypeptide, wherein said nucleic acid encodes the CARD domain of CARD-12X is read as open language, and therefore it is assumed for the purpose of compact prosecution that claim 2 is drawn to a nucleic acid encoding a polypeptide comprising a functional fragment of a CARD-containing polypeptide or comprising the CARD domain of CARD-12X. Thus claims 2 encompasses an unrelated nucleic acid molecule with unknown structure, provided it shares with SEQ ID NO:15 (CARD-12X) the CARD-12X domain.

Moreover, it is noted that a nucleic acid molecule encoding a functional fragment of a CARD-containing polypeptide, wherein said nucleic acid molecule **comprises** the nucleotide sequence of the CARD domain of CARD-12X polynucleotide encompasses an unrelated nucleic acid molecule with unknown structure, provided it shares with SEQ ID NO:15 (CARD-12X) the CARD-12X domain.

In addition, it is noted that an oligonucleotide comprising at least 15 contiguous nucleotides of SEQ ID NO:15 encompasses unrelated sequences with unknown structure, provided that said sequences share at least 15 contiguous nucleotides with SEQ ID NO:15.

It is further noted that a complement could be a partial or complete complement, wherein a partial complement could share with an oligonucleotide of SEQ ID NO:15 a few complementary nucleotides. Thus a complement of an oligonucleotide of SEQ ID NO:15 encompasses unrelated sequences with unknown structure.

The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an

invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of the hybridizing nucleic acid molecules, a nucleic acid encoding a polypeptide comprising the functional fragment of a CARD-containing polypeptide, the substantially the same nucleotide sequence as SEQ ID NO:15, or the oligonucleotide, or the complement thereof, per Lilly by structurally describing a representative number of the hybridizing nucleic acid molecules, a nucleic acid encoding a polypeptide comprising the functional fragment of a CARD-containing polypeptide, the substantially the same nucleotide sequence, the oligonucleotide, or the complement thereof, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the hybridizing nucleic acid molecules, a nucleic acid encoding a polypeptide comprising the functional fragment of a CARD-containing polypeptide, the substantially the same nucleotide sequence as SEQ ID NO:15, the oligonucleotide, or the complement thereof, in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any hybridizing nucleic acid molecules, any nucleic acid encoding a polypeptide comprising a functional fragment of a CARD-containing polypeptide, any substantially the same nucleotide sequence as SEQ ID NO:15, any oligonucleotide, or any complement other than SEQ ID NO:15, and the CARD domain thereof of SEQ ID NO:17, nor does the specification provide any physical or chemical characteristics of the hybridizing nucleic acid molecules, a nucleic acid encoding a polypeptide comprising the functional fragment of a CARD-containing polypeptide, the substantially the same nucleotide sequence as SEQ ID NO:15, the oligonucleotide, or the complement thereof, other than SEQ ID NO: 15, and the CARD-12X domain thereof of SEQ ID NO:17, wherein functional characteristics are coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single polynucleotide comprising SEQ ID NO: 15, and the CARD-12X domain thereof of SEQ ID NO:17, this does not provide a description of that would satisfy the standard set out in Enzo.

The specification also fails to describe the hybridizing nucleic acid molecules, a nucleic acid encoding a polypeptide comprising the functional fragment of a CARD-containing polypeptide, the substantially the same nucleotide sequence as SEQ ID

NO:15, the oligonucleotide, or the complement thereof, by the test set out in Lilly. The specification describes only a single polynucleotide comprising SEQ ID NO: 15, and the CARD-12X domain thereof of SEQ ID NO:17. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the hybridizing nucleic acid molecules, a nucleic acid encoding a polypeptide comprising the functional fragment of a CARD-containing polypeptide, the substantially the same nucleotide sequence as SEQ ID NO:15, the oligonucleotide, or the complement thereof, that is required to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. If Applicant could overcome the above 112, first paragraph above, claims 1-10, 14 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:15 or SEQ ID NO:17, **does not reasonably provide enablement for the claimed variants of SEQ ID NO:15 (CARD-12X polynucleotide) or the CARD-12X domain thereof (SEQ ID NO:17).** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-10, 14 are drawn to:

1) A nucleic acid molecule that **hybridizes** to the nucleic acid molecule of claim 1 **under moderately stringent hybridization conditions**, or a nucleic acid molecule that hybridizes to the nucleic acid molecule of claim 2 under moderately stringent hybridization conditions, wherein said nucleic acid molecule does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37, and a composition comprising said nucleic acid molecule effective to inhibit expression of a CARD-containing polypeptide. Said nucleic acid molecule is cDNA or mRNA (claims 1-2, 4, 7),

2) A nucleic acid molecule encoding a functional fragment of a CARD-containing polyppetide, wherein said nucleic acid molecule **comprises** the nucleotide sequence of the CARD domain of CARD-12X polynucleotide (claim 2)

3) A nucleic acid molecule comprising **substantially the same nucleotide sequence** as SEQ ID NO:15 (claim 3),

4) A vector and a host cell containing the nucleic acid molecule of claim 1 (claims 5-6),

5) An oligonucleotide **comprising** at least 15 contiguous nucleotides of SEQ ID NO:15, or the **complement** thereof, wherein said nucleic acid molecule does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37, wherein said oligonucleotide is labeled with a detectable marker, and a kit comprising said oligonucleotide (claims 8-10),

6) A method for producing a CARD-containing polypeptide, comprising expressing the cDNA of a nucleic acid molecule comprising **substantially the same nucleotide sequence** as SEQ ID NO:15 (claim 14).

The specification discloses that "moderately stringent hybridization" refers to conditions that permit target-nucleic acid to bind a complementary nucleic acid. The hybridized nucleic acid will "generally" have at least about 60%, 75%, 90% identity (p.32, last paragraph, bridging p.33).

The specification discloses that "substantially the same nucleotide sequence" refers to nucleic acids that hybridize to the reference polynucleotide under moderately or highly stringent conditions, or having at least 60%, 65%, ...or 99% identity to the reference nucleotide sequence (p.30, second paragraph).

It is noted that the claimed hybridizing nucleic acid molecules, or "substantially the same nucleotide sequence" as defined in the specification, encompass variants of SEQ ID NO:15, or variants of fragments thereof containing the CARD domain, with unknown structure, wherein said variants hybridize to SEQ ID NO:15 or fragments thereof containing the CARD domain via a common fragment, or have at least 60%, ...99% identity to SEQ ID NO:15.

Moreover, it is noted that a nucleic acid molecule encoding a functional fragment of a CARD-containing polyppetide, wherein said nucleic acid molecule comprises the nucleotide sequence of the CARD domain of CARD-12X polynucleotide encompasses an unrelated nucleic acid molecule with unknown structure, provided it shares with SEQ ID NO:15 (CARD-12X) the CARD-12X domain.

In addition, it is noted that an oligonucleotide comprising at least 15 contiguous nucleotides of SEQ ID NO:15 encompasses unrelated sequences with unknown structure, provided that said sequences share at least 15 contiguous nucleotides with SEQ ID NO:15.

It is further noted that a complement could be a partial or complete complement, wherein a partial complement could share with an oligonucleotide of SEQ ID NO:15 a few complementary nucleotides. Thus a complement of an oligonucleotide of SEQ ID NO:15 encompasses unrelated sequences with unknown structure.

The scope of the claims 1-10, 14 includes numerous structural variants. Applicants have not shown how to make and use the claimed variants which are capable of functioning or have the properties of the polynucleotide of SEQ ID NO:15, as that which is being disclosed.

The claimed variants have any type of substitution besides conservative substitution, at any nucleotide, throughout the length of the polynucleotide, as well as insertions and deletions. The specification and the claims do not place any limit on which nucleotide to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of nucleotides replacing the original nucleotides. Thus the scope of the claims includes structural variant nucleotide sequences encoding numerous structural variant polypeptide. The specification and the claims do not provide any guidance as to which nucleotides to be substituted, or to which type of substitution besides conservative substitution, or which

nucleotide could be deleted or inserted so that the claimed polynucleotide could function as contemplated.

One cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the claimed variants would have biological activity or properties related to that of SEQ ID NO:15. The following teaching of the art, although drawn to proteins, would apply as well the claimed polynucleotide variants of SEQ ID NO:15, because polynucleotide sequences encode proteins. It is well known in the art that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative

substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

The specification does not disclose how to make the claimed nucleic acid molecules, such that they would function or have the properties as claimed, or how to use said nucleic acid molecules if they did not have the function or properties claimed.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph above, claims 2, 7 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid molecule encoding a fragment of CARD-12X polypeptide comprising the CARD-domain of CARD-12X , **does not reasonably provide enablement for** a nucleic acid molecule encoding **a functional fragment** of a

CARD-containing polypeptide, wherein said nucleic acid molecule comprises the nucleotide sequence of the CARD domain of CARD-12X polynucleotide, or encoding the CARD domain of CARD-12X polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 2, 7 are drawn to a nucleic acid molecule encoding a functional fragment of a CARD-containing polypeptide, wherein said nucleic acid molecule comprises the nucleotide sequence of the CARD domain of CARD-12X polynucleotide, or encoding the CARD domain of CARD-12X polypeptide.

The disclosure of the specification has been set forth above.

The specification further discloses that "functional" fragments refer to a polypeptide that exhibits biological activities similar to at least a portion of a CARD-containing polypeptide of the invention (p.20, second paragraph). The specification further discloses that biological activies of a CARD-containing polypeptide "include, for example" the ability to bind to a CARD-associated polypeptide,(e.g. a caspase or procaspase), to another CARD-containing polypeptide, to a cytoskeletal component, or to another protein, thereby altering apoptosis, NF-KB induction, cytokine processing, cytokine receptor signaling, caspase-mediated proteolysis, cytoskeletal integrity or anoikis..

It is noted that no function has been elucidated for the CARD domain of CARD-12.

It is further noted that the definition of the term biological activies of a CARD-containing polypeptide is non-limiting. Thus a functional fragment could have any biological activity, for example a whole universe of unrelated activities, such as the activity of a polymerase or an RNAse etc...

One cannot extrapolate the teaching in the specification to the scope of the claims. The function of SEQ ID NO:15 is based on the assumption that via the putative CARD-12X domain, the encoded polypeptide of SEQ ID NO:16 would bind to caspases and either activates or inhibits caspases. However there is no evidence that the putative CARD-12X domain of SEQ ID NO:16 would have the property of a CARD, conferring the binding ability to caspase, nor any evidence that after binding to caspases, SEQ ID NO:16 somehow could activate or inhibit caspases, a step necessary for inducing or inhibiting apoptosis. It is well known in the art that a CARD-containing polypeptide activates a caspase by forming a hetero-oligomer with the caspase and in this complex, the CARD-containing polypeptide allosterically upregulates the caspase activity (Shiozaki E N, 2002, Proceed Natl Acad Sci, USA, 99 (7): 4197-202). It is also well known in the art that oligomerization of a caspase is induced by the CARD-containing polypeptide, and is required for casapse activation (Lee S H et al, 2001, J Biol Chem, 276(37): 34495-500). The specification however has not shown that the CARD-12X protein encoded by the claimed polynucleotide could induce the oligomerization of caspases upon interaction with caspases via the CARD-12X domain. Further, even if the putative CARD domain of the CARD-12X protein has the property of a CARD, one cannot predict that the CARD-12X protein

could induce apoptosis, because not all CARD-containing polypeptides would induce apoptosis. For example, the CARD domain of CARD-containing RAIDD polypeptide does not induce apoptosis upon overexpression (Shaerwin-Whyatt LM et al, 2000, Cell Death and Differentiation, 7: 155-165, especially page 162, first column). Moreover, there is no indication that the CARD-12X protein interacts and regulates NF-κB activation, or regulates cytokine processing, cytokine receptor signaling, caspase-mediated proteolysis, cytoskeletal integrity or anoikis, because there is no evidence that the putative CARD-12X domain has the property of a CARD domain, or regulates NF-kB activation, cytokine processing, cytokine receptor signaling, caspase-mediated proteolysis, cytoskeletal integrity or anoikis, and because not any protein would regulate NF-kB activation, cytokine processing, cytokine receptor signaling, caspase-mediated proteolysis, cytoskeletal integrity or anoikis..

Moreover, one cannot predict that the claimed functional fragment would have any biological activity, because there is no indication that the claimed functional fragment has a function correlated with a whole universe of unrelated activities, such as the activity of a polymerase or an RNAase etc,,

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

3. If Applicant could overcome the above 112, first paragraph above, claim 6 is still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell comprising a vector comprising SEQ ID NO:15, does not reasonably provide enablement for **a host cell** comprising a vector comprising SEQ

ID NO:15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 6 is drawn to a host cell comprising SEQ ID NO:15 (CARD-12X polynucleotide), a nucleic acid molecule encoding CARD-12X polypeptide, or a nucleic acid molecule that hybridizes to SEQ ID NO:15 (CARD-12X polynucleotide), or a nucleic acid molecule encoding CARD-12X polypeptide .

The specification discloses that the recombinant cells are generated by introducing into a host cell a vector containing a CARD-encoding nucleic acid molecule (p.43, last paragraph, bridging p.44). The specification contemplates gene therapy comprising administering a vector containing a CARD-encoding nucleic acid or an antisense sequence thereof (p.49, first paragraph)..

Thus claim 6 encompasses a host cell in vivo comprising a vector comprising SEQ ID NO:15 or antisense sequence thereof, obtained from gene therapy, as contemplated.

On cannot extrapolate the teaching in the specification to the scope of the claim. The state of the gene therapy art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene

therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Thus based on the teaching in the art and in the specification, one cannot predict that a host cell in vivo comprising a vector comprising SEQ ID NO:58 could be obtained from gene therapy, as contemplated.

Thus based on the above unpredictability of gene therapy, as taught in the art, and in view of the lack of any objective evidence of successfully obtaining in vivo host cell comprising SEQ ID NO:15 or antisense sequence thereof, it would be undue experimentation for one of skill in the art to practice the claimed invention.

It is noted that this rejection could be obviated by amending the claim 6 for example to recite "an isolated host cell".

4. If Applicant could overcome the above 112, first paragraph above, claim 7 is still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:15 (CARD-12X polynucleotide) or the CARD-12X domain thereof (SEQ ID NO:17), **does not reasonably provide enablement for a nucleic acid molecule effective to inhibit expression of a CARD-containing polypeptide.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 7 is drawn to a composition comprising a nucleic acid molecule "effective to inhibit expression of a CARD-containing polypeptide", wherein said nucleic acid molecule comprises a nucleic acid molecule that hybridizes to the nucleic acid molecule of claim 1 under moderately stringent hybridization conditions, or a nucleic acid molecule that hybridizes to the nucleic acid molecule of claim 2 under moderately stringent hybridization conditions, wherein said nucleic acid molecule does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37.

Claim 7 reads on a composition comprising a nucleic acid molecule effective to inhibit expression of SEQ ID NO:15 **in vivo**, as contemplated, i.e. gene therapy, using an antisense of SEQ ID NO:15.

Claim 7 also encompasses a composition comprising a nucleic acid molecule effective to inhibit expression of "**any**" CARD-containing polypeptide, wherein said nucleic acid molecule comprises a nucleic acid molecule that hybridizes to the nucleic acid molecule of claim 1 under moderately stringent hybridization conditions, or a nucleic acid molecule that hybridizes to the nucleic acid molecule of claim 2 under moderately stringent hybridization conditions, wherein said nucleic acid molecule does not consists of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37.

The disclosure of the specification has been set forth above.

On cannot extrapolate the teaching in the specification to the scope of the claim. The state of the gene therapy art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable, *supra*. Further, It is well known in the art that antisense therapy is unpredictable. Branch, AD, 1998, TIBS 23: 45-50 teaches that it is very difficult to predict what portions of an RNA molecule will be accessible to an antisense sequence *in vivo*, and therefore, rational design of antisense molecule is not possible. Branch further teaches that although antisense oligonucleotides could be screened *in vitro*, it is not clear whether the identified antisense oligonucleotides are effective *in vivo*, and that *in vitro* studies will not always predict *in vivo* efficacy (p.49, first column, last

paragraph, bridging second paragraph, and last column, second paragraph). In addition, Branch also teaches that although some antisense molecules had some clinical value through non-antisense effects, the non-antisense effects are not predictable and these effects must be explored on a case-by-case basis (p.50, first column). Further, even if an antisense oligonucleotide could be successfully used *in vitro* to inhibit the expression of a gene, it is unpredictable that said antisense oligonucleotide could be successfully used *in vivo*, because 1) successful application of antisense therapy *in vivo* has been extremely limited, and that there are only a few reports of modulation of various pathological conditions by antisense therapy in rodents, and 2) even if the biological significant amounts of antisense molecules reach target cells, and bind to selected target sites on mRNA, a subsequent effect on regulation of translation is not guaranteed, as taught by Weiss, 1998, US 5,840,708.

Thus given the unpredictability of the behavior and effect of antisense therapy, and the unpredictability of gene therapy, one cannot predict that the claimed hybridizing polynucleotides could be used successfully for in vivo inhibiting expression of SEQ ID NO:15.

Further, one cannot predict that the polynucleotides that hybridize to SEQ ID NO:15 or fragments thereof would be effective in inhibiting expression of any CARD-containing polypeptide. One would not expect that any CARD-containing polynucleotides have the same structure as SEQ ID NO:15, and thus one would not know how to make and use an antisense sequence from SEQ ID NO:15, that would inhibit expression of a CARD-containing polypeptide having unrelated structure.

REJECTION UNDER 35 USC 102(b or e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting

directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

1. Claims 1-6, 14 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2002/0081636, or the parent case WO200159065-A2, both of which has as priority Application 60/181159, filed on Feb 09, 2000.

Claims 1-6, 14 are drawn to:

1) A nucleic acid molecule encoding a functional fragment of a CARD-containing polyppetide, wherein said nucleic acid molecule comprises the nucleotide sequence of the CARD domain of CARD-12X polynucleotide, or encoding the CARD domain of CARD-12X polypeptide (claim 2).

2) A nucleic acid molecule that hybridizes to the nucleic acid molecule encoding the amino acid sequence of CARD-12X (the polypeptide of SEQ ID NO:16), or the polynucleotide of SEQ ID NO:15, under moderately stringent hybridization conditions (claim 1), or a nucleic acid molecule that hybridizes to the nucleic acid molecule of claim 2 under moderately stringent hybridization conditions, wherein said nucleic acid molecule does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37 (claim 2). Said nucleic acid molecule of claim 1 is cDNA or mRNA (claim 4),

3) A nucleic acid molecule comprising substantially the same nucleotide sequence as SEQ ID NO:15 (claim 3),

3) A vector and a host cell containing the nucleic acid molecule of claim 1 (claims 5-6),

The specification discloses that "substantially the same nucleotide sequence" refers to nucleic acids that hybridize to the reference polynucleotide under moderately or highly stringent conditions (p.30, second paragraph).

In view of the disclosure in the specification, claim 3 encompasses a nucleic acid that hybridizes to SEQ ID NO:15 under moderately or highly stringent conditions.

US 2002/0081636 or WO200159065-A2 teaches a predicted polynucleotide cDNA sequence, SEQ ID NO:4 in figure 2A-C, which is 3417 nucleotides in length, and comprises a sequence which is 100% similar to the full length of SEQ ID NO:17, the CARD-12X domain polynucleotide, from nucleotide 1 to nucleotide 176, as shown by MPSRCH sequence similarity search (MPSRCH search report, 2004, us-10-032-159a-17.rnpb, p.2-3 and us-10-032-159a-17.rng, p.2-3). SEQ ID NO:4 of US 2002/0081636 is the same as the polynucleotide sequence from Fig 1 of the prior Application 60/181159.

The polynucleotide of US 2002/0081636 or WO200159065-A2 encodes a protein which is 100% similar to the full length of SEQ ID NO:18, the CARD-12X domain polypeptide, from amino acid 1 to amino acid 92, as shown by MPSRCH sequence similarity search (MPSRCH search report, 2004, us-10-032-159a-18, rag, p.3). See also amino acids 16-107 encoded by the polynucleotide sequence of Fig 1 of the prior Application 60/181159.

The sequence taught by US 2002/0081636 or WO200159065-A2 would hybridize to the claimed sequence of SEQ ID NO:15, or SEQ ID NO:17, and certainly comprises

the CARD-12X domain polynucleotide (SEQ ID NO:17) or encoding the CARD-12X domain polypeptide (SEQ ID NO:18). Further, since SEQ ID NO:4 of prior art is 3417 nucleotides in length, it certainly does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37, which range from 162 to 2176 nucleotides in length,

US 2002/0081636 also teaches expression vectors and host cells containing a nucleic acid encoding CARD-14, and a method for producing CARD-14 protein, by expression of CARD-14 polynucleotide (p.21-23)

Thus the sequence, vector, host cell, and the method for producing a CARD-containing polypeptide taught by US 2002/0081636 seem to be the same as claimed sequence, vector, host cell and the method for producing a CARD-containing polypeptide.

The reference does not specifically teach that the polynucleotide hybridizes to the nucleic acid sequence of SEQ ID NO:15 or fragments thereof containing the CARD-12X domain, wherein said nucleic acid molecule does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37, or is substantially the same nucleotide sequence as SEQ ID NO:15, or comprises the CARD-12X domain polynucleotide or encoding the CARD-12X domain polypeptide. However, the claimed nucleic acid molecule appears to be the same as the prior art polynucleotide. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different

from those taught by the prior art. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

2. Claim 8 is rejected under 35 U.S.C. 102(e) (pre-AIPA) as being anticipated by US 6,599,697 B1.

Claim 8 is drawn to an oligonucleotide comprising at least 15 contiguous nucleotides of SEQ ID NO:15, or the complement thereof, wherein said nucleic acid molecule does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37.

US 6,599,697 B1 teaches a primer of SEQ ID NO:23, for amplifying gene III (figure 16 legend), which has 39 nucleotides in length, and is 100% similar to the claimed SEQ ID NO:15, from nucleotide 67 to nucleotide 84, as shown by MPSRCH sequence similarity search (MPSRCH search report, 2004, us-10-032-159a-15.oligo100.rni, p.1).

The polynucleotide taught by US 6,599,697 B1 comprises at least 15 contiguous nucleotides of SEQ ID NO:15. Further, since the polynucleotide taught by US 6,599,697 B1 has 39 nucleotides in length, it certainly does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37, which range from 162 to 2176 nucleotides in length,

Thus the polynucleotide taught by US 6,599,697 B1 seems to be the same as the claimed oligonucleotide.

Further, given the polynucleotide taught by US 6,599,697 B1, one would readily envision a complement thereof.

Although the reference does not specifically teach an oligonucleotide comprising at least 15 contiguous nucleotides of SEQ ID NO:15, or the complement thereof, wherein said nucleic acid molecule does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37, however, the claimed oligonucleotide appears to be the same as the prior art polynucleotide. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

REJECTION UNDER 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,599,697 B1, in view of Sambrook et al, eds, 1989, Molecular Cloning, A laboratory manual, Second edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, p.11.31-11.32.

Claims 9-10 are drawn to an oligonucleotide comprising at least 15 contiguous nucleotides of SEQ ID NO:15, or the complement thereof, wherein said nucleic acid

molecule does not consist of the nucleotide sequence set forth as SEQ ID NO:19 or 21-37, wherein said oligonucleotide is labeled with a detectable marker, and a kit comprising said oligonucleotide.

The teaching of US 6,599,697 B1 has been set forth above.

US 6,599,697 B1 does not teach labeling the polynucleotide with a detectable marker, or a kit comprising said polynucleotide.

Sambrook et al teach labeling of oligonucleotides with a radiolabel.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to label the primer taught by US 6,599,697 B1, using the method taught by Sambrook et al. The motivation is for detecting the presence of the polynucleotide comprising said primer, such as gene III, taught by US 6,599,697 B1.

Further, it would have been obvious to formulate said labeled primer in a kit for commercial application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

PATENT EXAMINER

March 25, 2004